EXHIBIT 228

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Central Region
New Jersey District

North Brunswick Resident Post
120 North Center Drive
North Brunswick, NJ 08902
(732) 940-8996

November 17, 2006

Divya Patel, President
Actavis Totowa LLC
101 East Main Street
Little Falls, New Jersey 07024

Dear Mr. Patel:

We are enclosing a copy of the establishment inspection report (EIR) for the inspection conducted at your premises at 4 Taft Road, Totowa, New Jersey on September 18, 2006 et al. on behalf of the U.S. Food and Drug Administration (FDA). This report is being provided to you for information purposes.

This new procedure is applicable to EIRs for inspections completed on or after April 1, 1997. For those inspections completed prior to the above date, a copy of the EIR may still be made available through the Freedom of Information Act (FOIA).

The Agency is working to make its regulatory process and activities more transparent to the regulated industry. Releasing this EIR to you is part of this effort. The copy being provided to you comprises the narrative portion of the report; it reflects redactions made by the Agency in accordance with the FOIA and 21 C.F.R. Part 20. This, however, does not preclude you from requesting and, possibly, obtaining any additional information under FOIA.

If there is any question about the released information, feel free to contact Ray Abrahams at (973) 526-6002 or write to:

U.S. Food and Drug Administration
10 Waterview Blvd.
Parsippany, New Jersey 07054

Sincerely,

Nancy Rolli

Nancy Rolli
Supervisory Investigator

Establishment Inspection Report	FEI:	3003450194
Actavis Totowa LLC	EI Start:	09/18/2006
Totowa, NJ 07512-1006	EI End:	10/11/2006

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SUMMARY

This inspection of a pharmaceutical packaging, labeling and testing facility was conducted under a Special Audit Assignment under FACTS Assignment # 717181, Operation ID # 2749476. A general GMP inspection was also conducted as part of NWJ-DO FY06 Drug Work Plan (FACTS Assignment # 3474850, Operation ID # 2780701 was reported under Assignment # 717181, Operation ID # 2749476). Inspectional guidance was afforded through Compliance Program Guidance Manual 7356.002: Drug Manufacturing Inspection.

The previous inspection of 10/26/04, provided coverage of the Quality and Packaging & Labeling Systems. No deficiencies were noted and the inspection was classified NAI.

The Quality, Packaging & Labeling, Laboratory Control, Facilities & Equipment and Materials Systems were covered during the current inspection. An FDA 483, Inspectional Observations, was issued at the closeout meeting regarding deficiencies in the areas of laboratory investigations,

method validations and cleaning validations. In addition, a discussion was held with management regarding warehousing procedures, the establishment of solution stabilities for the testing of related substances, equipment qualifications and preventative maintenance. Corrections were promised for all observations and discussion items.

ADMINISTRATIVE DATA

Inspected firm:	Actavis Totowa LLC
Location:	4 Taft Road Totowa, NJ 07512-1006
Phone:	(973) 890-1555
FAX:	
Mailing address:	4 Taft Road Totowa, NJ 07512-1006
Dates of inspection:	9/18/2006, 9/19/2006, 9/20/2006, 9/26/2006, 9/27/2006, 9/28/2006, 10/2/2006, 10/4/2006, 10/11/2006
Days in the facility:	9
Participants:	Kristy A. Zielny, Investigator

On 9/18/06, I, Investigator Kristy A. Zielny, presented my credentials and issued an FDA 482, Notice of Inspection, to Mr. Divya Patel, President. Mr. Patel indicated he is the most responsible individual for this site. Mr. Jasmine Shah, Vice President, Regulatory and Quality Compliance, and Mr. Nasrat Hakim, Vice President, Quality and Compliance US, were also present for the initiation of the inspection. A "Resources for FDA Regulated Businesses" form was also presented at this time. I explained that the purpose of my visit was to provide an audit to applications [redacted] as well as GMP inspectional coverage.

Mr. Jasmine Shah provided all requested information and documentation as requested and arranged meetings with additional personnel as necessary. Also participating in the inspection were:

Ashok Nigalaya, Senior Vice President, Scientific Affairs
Ashesh Dave, Director of Packaging and Labeling
Kirit Patel, Director Analytical Development Laboratory
Nasrat Hakim, Vice President of U.S Quality
Gudrun Eyjolfsdottir, Global VP of Quality and Compliance Actavis Group
Varsha Bhagat, Label Room Coordinator

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Gaurang Pandya, Senior Scientist, Analytical Research
Tarak Shah, Senior Scientist, Analytical Research
Nilesh Patel, TCCS System Manager
Dmitriy Kalika, Manager, Information Systems

On 10/11/06, an FDA 483, Inspectional Observations, was issued to Mr. Divya Patel, President. In addition, a discussion was held with management both during the inspection and again at the closeout meeting. Corrections were promised for all observations and discussion items. A written response to the 483 observations was promised as well.

HISTORY

Actavis Totowa LLC currently consists of two sites. This site, at located 4 Taft Road, Totowa, NJ, is responsible for all packaging, labeling, distribution, packaging component receiving, R&D, testing of Exhibit Batches and stability testing. The second site is located at 101 East Main Street, Little Falls, NJ, and is responsible for raw material receiving, all manufacturing operations and most of the analytical testing. A third site, located at 900 Riverview Drive, Totowa, NJ, is expected to begin manufacturing operations within the next 60 days.

This site, previously operating as Amide Pharmaceutical, Inc. was founded in 1983 and was acquired by Actavis on July 27, 2005. The name legally changed to Actavis Totowa LLC on May 15, 2006. Actavis Totowa LLC is a wholly owned subsidiary of Actavis Group, which was founded in 1956 and is based in Reykjavick, Iceland.

All regulatory correspondence should be addressed to Mr. Divya Patel, President of Actavis Totowa LLC, at 101 East Main Street, Little Falls, NJ 07424. Mr. Divya Patel is the most responsible individual at both 4 Taft Road and 101 East main Street, Little Falls. The Little Falls facility is also the current headquarters for Actavis Totowa LLC. Mr. Sigadur Olaffson, President of Actavis U.S. Operations, should also be copied on all correspondence at 900 Riverview Drive, Totowa, NJ.

This facility currently operates 7:30 AM through 4:00 PM, Monday through Friday, with overtime on Saturdays as needed. There are approximately 102 individuals employed at this facility. This site consists of one building: the first floor accommodates the warehouse and packaging and labeling operations and the second floor houses the Quality Control laboratory. The floor plan of the 4 Taft Road, Totowa facility is attached as **Exhibit 1**.

Major customers include [redacted]

The annual volume of sale for Actavis Totowa LLC, was estimated to be [redacted] in 2005. The estimated volume of sale for this year will be approximately [redacted]

INTERSTATE COMMERCE

Mr. Jasmine Shah stated approximately [redacted] of the business is conducted interstate.

JURISDICTION AND OPERATIONS

Actavis Totowa LLC (Taft Road, Totowa) is responsible for all packaging, labeling and distribution of generic pharmaceutical products manufactured at the Little Falls facility. The Taft Road facility is also responsible for testing of all ANDA Exhibit Batches as well as stability testing of these batches and occasionally stability testing of commercial product. Dosage forms packaged, labeled at this facility include prompt release tablets and capsules and extended release tablets. A list of products was provided and is attached as **Exhibit 2.**

INDIVIDUAL RESPONSIBILITY

The following are the key officials of Actavis Totowa LLC:

Mr. Divya Patel, President and CEO

Mr. Divya Patel is the most responsible individual at the 4 Taft Road, Totowa facility as well as the Little Falls site. His responsibilities include overall operations, sales, marketing and all other business aspects.

Mr. Ashok Nigalaya, Senior Vice President, Scientific Affairs

Mr. Nigalaya is the most responsible individual with respect to the scientific aspects of the business. His responsibilities include overseeing all of the laboratory, manufacturing and technical support. He is primarily located at the Little Falls site.

Mr. Apurva Patel, Project Management, Research and Development

Mr. Apurva Patel is responsible for Product Development.

Mr. Deepak Bhalla, Director of Technical Affairs

Mr. Bhalla's responsibilities include research and development, special projects and difficult formulations.

Mr. Ashesh Dave, Director of Packaging and Labeling
Mr. Dave is responsible for overseeing all packaging and labeling operations.

Mr. Jasmine Shah, Vice President, Regulatory and Quality Compliance
Mr. Shah is responsible for overseeing all Regulatory Affairs and quality compliance issues at both the 4 Taft Road and Little Falls facilities.

Mr. Bharat Patel, Vice President Materials Management
Mr. Bharat Patel is responsible for all purchasing for the Actavis Totowa facilities.

Mr. Manoj Patel, Director of Engineering
Mr. Manoj Patel is located offsite and is responsible for HVAC, facility designs, and all utilities.

Mr. Kirit Patel, Director Analytical Development Laboratory
Mr. Kirit Patel is responsible for method development and ANDA submissions.

Mr. Devji Kumbhani, Director of Product Formulations
Mr. Kumbhani is responsible for the development of new products.

Mr. Rick Dowling, Director of Manufacturing Operations
Mr. Dowling is responsible for overseeing all manufacturing operations at the Little Falls facility.

Mr. Satish Laroia, Director of Manufacturing Compliance
Mr. Laroia is responsible for batch record reviews, calibration, batch control, cGMP training and safety training. Mr. Laroia is located at the Little Falls facility

Mr. Frank Carlucci, Director of Quality Control Laboratory
Mr. Carlucci is located at the Little Falls facility and is responsible for overseeing all quality control operations for raw materials, finished products and stability products.

Mr. Apurva Patel, Mr. Rick Dowling, Mr. Satish Laroia, Mr. Frank Carlucci, Mr. Ashesh Dave, Mr. Jasmine Shah, Mr. Bharat Patel, Mr. Manoj Patel, Mr. Kirit Patel and Mr. Devji Kumbhani all report to Mr. Ashok Nigalaya, Senior Vice President, Scientific Affairs. Mr. Deepak Bhalla and Mr. Ashok Nigalaya report directly to Mr. Divya Patel, President and CEO. Mr. Divya Patel reports to Mr. Sigadur Olaffson, President of Actavis U.S. Operations. Mr. Sigadur Olaffson reports to Mr. Robert Weissman, CEO of Actavis Worldwide.

The most responsible individual at this site is Mr. Divya Patel, President and CEO. All regulatory correspondence should be addressed to his attention at 101 East Main Street, Little Falls, NJ 07424. Mr. Sigadur Olaffson, President of Actavis U.S. Operations should also be copied on all correspondence at 900 Riverview Drive, Totowa, NJ.

CHANGES IN OPERATIONS AND PERSONNEL

Since the previous inspection of October 2004, the following changes have occurred

Changes in operation

Mr. Ashesh Dave was promoted to Director of Packaging in 2005.

Mr. Kirit Patel was promoted from Manager of Analytical R&D to Director of Anal 2005.

Mr. Devji Kumbhani became Director of Product Development in 2005.

Mr. Dan Bitler became QA Director in 2004.

Mr. Leroy Ludner became Associate Director of Quality Compliance in 2004.

Mr. Jasmine Shah, was promoted from Director of Regulatory Affairs to Vice President of Regulatory and Quality Compliance in 2005 and was also designated as Vice President of U.S. Regulatory and Medical Affairs in February 2006.

Mr. Ashok Nigalaya was promoted from Vice President of Operations to Senior Vice President of Scientific Affairs in 2005.

Additional changes are to take place in the near future with respect to personnel. A number of new positions are expected to be filled including those of Site Head of Quality, Director of Regulatory Affairs, Quality Assurance Director, two positions in Quality Assurance, three to four Quality Control Supervisory positions. Furthermore, the reporting structure will change such that Operations reports to the Site Head of Quality, and Quality will be reporting to both the President/CEO and to Corporate Head of Quality U.S.

Organizational charts were provided for Actavis Totowa LLC and are attached as **Exhibit 3 and Exhibit 4**. Exhibit 3 shows the organization prior to the inspection of the Little Falls facility in July 2006. Exhibit 4 shows the re-organization post-QSIP (quality systems improvement plan) assessment.

Changes in operations include the discontinuation of a number of products including: [redacted]

The most responsible individual at this site is Mr. Divya Patel, President and CEO. All regulatory correspondence should be addressed to his attention at 101 East Main Street, Little Falls, NJ 07424. Mr. Sigadur Olaffson, President of Actavis U.S. Operations should also be copied on all correspondence at 900 Riverview Drive, Totowa, NJ.

CHANGES IN OPERATIONS AND PERSONNEL

Since the previous inspection of October 2004, the following changes have occurred in personnel:

Mr. Ashesh Dave was promoted to Director of Packaging in 2005.

Mr. Kirit Patel was promoted from Manager of Analytical R&D to Director of Analytical R&D in 2005.

Mr. Devji Kumbhani became Director of Product Development in 2005.

Mr. Dan Bitler became QA Director in 2004.

Mr. Leroy Ludner became Associate Director of Quality Compliance in 2004.

Mr. Jasmine Shah, was promoted from Director of Regulatory Affairs to Vice President of Regulatory and Quality Compliance in 2005 and was also designated as Vice President of U.S. Regulatory and Medical Affairs in February 2006.

Mr. Ashok Nigalaya was promoted from Vice President of Operations to Senior Vice President of Scientific Affairs in 2005.

Additional changes are to take place in the near future with respect to personnel. A number of new positions are expected to be filled including those of Site Head of Quality, Director of Regulatory Affairs, Quality Assurance Director, two positions in Quality Assurance, three to four Quality Control Supervisory positions. Furthermore, the reporting structure will change such that Operations reports to the Site Head of Quality, and Quality will be reporting to both the President/CEO and to Corporate Head of Quality U.S.

Organizational charts were provided for Actavis Totowa LLC and are attached as **Exhibit 3 and Exhibit 4**. Exhibit 3 shows the organization prior to the inspection of the Little Falls facility in July 2006. Exhibit 4 shows the re-organization post-QSIP (quality systems improvement plan) assessment.

Changes in operations include the discontinuation of a number of products including: [redacted]

[redacted]

An additional packaging line has also been added since the previous inspection. This is the first blister packaging line in the facility.

MANUFACTURING CODES

Manufacturing codes were explained to be assigned as follows:

The first digit indicates the year of production (6 = 2006). The following four digits are a consecutive number representing the number batch produced in that year (0012 would indicate this was the 12th batch manufactured in that particular year). The following character is a letter indicating if the batch was divided by different logos or customers ("A" would indicate the first logo or customer and "B" would indicate the second). The last digit would be indicative of the packaging configuration ("1" would represent the first packaging configuration and "2" would indicate the second).

The prefix "RBR" is present for research and development batches and ANDA submission batches.

INSPECTIONAL COVERAGE

The Quality, Packaging & Labeling, Laboratory Control, Facilities & Equipment System and Materials Systems were covered during the current inspection.

Items reviewed during this inspection include, but were not limited to:

Facility Tour
Standard Operating Procedures (SOPs)
Receiving and Warehousing Procedures
Equipment Cleaning and Usage Logs
Equipment Calibration and Preventive Maintenance
Analytical Raw Data (ANDA submission batches)
Packaging and Labeling Records
OOS and Out of Trend Investigations

Laboratory Investigations
Change Controls
Complaints
GMP Training
Equipment Qualifications
Cleaning Validations
Recovery Studies
Method Validations
Stability Data
Laboratory Notebooks
TotalChrome Data Acquisition System

DATA AUDIT

FACTS Assignment # 717181, Operation ID 2749476 requested a special data audit of ANDAs [redacted] which were for [redacted] respectively. Data submitted in the applications were compared to raw data in laboratory notebooks and with data stored in the TurboChrom Data Acquisition System. No discrepancies were noted between the submitted data and the raw data reviewed.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

Present for the closeout meeting on 10/11/06, were Mr. Divya Patel, President and CEO, Mr. Ashok Nigalaya, Senior Vice President, Scientific Affairs, Mr. Jasmine Shah, Vice President, Regulatory and Quality Compliance, Mr. Nasrat Hakim, Vice President of U.S Quality, and Ms. Gudrun Eyjolfsdottir, Global VP of Quality and Compliance Actavis Group.

Observations listed on form FDA 483

LABORATORY CONTROL SYSTEM

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OBSERVATION 1

Deviations from written specifications, test procedures, and laboratory mechanisms are not justified.

Specifically, upon receipt of atypical data in the analytical laboratory, re-tests are performed without invalidating the original results. In addition, the results of re-testing are reported and original results are ignored. For example:

a) After receiving a "high dissolution value" of [redacted] drug dissolved for tablet # 5 in the dissolution testing of [redacted] no assignable cause could be identified and the analysis was re-performed with freshly prepared standard and sample solutions. The original results were ignored and the re-test results were reported.

b) "Suspect test results" in the related substance testing of [redacted] were attributed to the [redacted] µm filter used to filter the sample solution. The sample chromatogram for the [redacted] pack size contained unknown peaks at [redacted] minutes and the sample chromatogram for the [redacted] pack size had a peak at the expected retention time of [redacted] These results were received on 4/27/06, but no investigation was initiated until 5/17/06, in which the results were reported as "suspect test results" rather than "out of specification results". The filter study completed on 5/31/06 provides an explanation for unknown peaks at approximately [redacted] when the filter is not pre-conditioned, but not for a peak appearing at the expected retention time of [redacted] The original results were discarded and the repeat test results were reported.

c) When "comparatively lower" results were received during the related substances testing of [redacted] room temperature stability test point, an investigation could find no cause to the out of trend data. The [redacted] room temperature samples (both [redacted] packs) were re-tested, were found within the typical trend and were reported without invalidating the original results.

d) In the testing of [redacted] for chromatographic purity at the [redacted] room temperature test point, the [redacted] count bottles were found "significantly less compared to the previous stability stations." The investigation was inconclusive, the samples were re-tested and re-testing results were found to be comparable with the previous stability station results. The results of re-testing were reported without invalidating the original results.

Reference: 21 CFR 211.160(a)

Supporting Evidence and Relevance:

In reviewing Laboratory Investigation Reference # [redacted] **(Exhibit 5)**, I noted that after receiving a "high dissolution value" of [redacted] drug dissolved for tablet # 5 in the dissolution testing of [redacted] on 7/28/05, no assignable cause could be identified. The analysis was re-performed with freshly prepared standard and sample solutions on 7/29/05 **(Exhibit 6)**. The original results were ignored and the re-test

results were reported. I explained that the original results can not be ignored and should not have been replaced with re-test results.

Upon reviewing OOS Investigation Number [redacted] **(Exhibit 7)**, which referred to an "Investigation Report For The Suspected Test Result **(Exhibit 8)**", it was noted that "Suspect test results" in the related substance testing of [redacted] were attributed to the [redacted] µm filter used to filter the sample solution. The sample chromatogram for the [redacted] pack size contained unknown peaks at [redacted] **(Exhibit 8, pages 1 and 6)** and the sample chromatogram for the [redacted] pack size had a peak at the expected retention time of [redacted] specification is NMT [redacted]%) **(Exhibit 8, pages 1 and 5)**. These results were received on 4/27/06, but no investigation was initiated until 5/17/06, in which the results were reported as "suspect test results" rather than "out of specification results" **(Exhibit 7, page 1 and Exhibit 8, page 1)**. The reason provided for not initiating the investigation immediately was explained to be an error made by the analyst in incorrectly identifying the [redacted] as an unknown for the [redacted] pack size **(Exhibit 9, pages 5 and 6)**. The error was not noticed by the 2nd analyst who checked the 1st analyst's work. The error was instead noted by the Supervisor upon reviewing the data prior to submission of this data for the ANDA for [redacted] **(Exhibit 9, pages 5 and 6)**. I explained that an investigation should have been initiated prior to this because of the unknown peaks present in the [redacted] pack size.

The filter study completed on 5/31/06 **(Exhibit 10)** provides an explanation for unknown peaks at approximately [redacted] when the filter is not pre-conditioned, but not for a peak appearing at the expected retention time of [redacted] Management explained that the unknown peaks can elute at any retention time depending on how much of the solution is discarded when the filter is not pre-conditioned. I explained that the filter study consistently demonstrated that unknown peaks occurred at approximately the same retention times of [redacted] and that in no cases were peaks observed at [redacted] as observed in the [redacted] pack size of [redacted] Batch # [redacted] The original results were discarded and the repeat test results were reported **(Exhibit 11)**.

In reviewing Investigation [redacted] it was noted that the investigation could find no cause to "comparatively lower" results that were received during the related substances testing of [redacted] room temperature stability test point **(Exhibit 12)**. In order to verify the atypical results, the [redacted] room temperature samples were reanalyzed. The results of the reanalysis were found to be within the typical trend and it was decided to exclude the original results received on January 22, 2005 from the stability study results and to replace them with the retest results from January 26, 2005 **(Exhibit 12, page 4)**. I explained that the original results should not have been discarded as there was no reason for invalidating them.

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Investigation [redacted] stated that in the testing of [redacted] for chromatographic purity at the [redacted] room temperature test point, the BP Impurity D value for both [redacted] count and [redacted] count bottles were found "significantly less compared to the previous stability stations" **(Exhibit 13)**. The investigation was inconclusive, and the [redacted] room temperature stability samples were re-tested. Re-testing results were found to be comparable with the previous stability station results **(Exhibit 14)**. The results of re-testing were reported without invalidating the original results.

Discussion with Management:

I explained that when an assignable cause is not found during the investigation of an atypical result, retesting results may not be reported instead of the original results. I explained that the original results remain valid and must be reported unless the investigation can show that the original results are the result of a laboratory error such as in sample preparation or testing. I explained that I reviewed a number of investigations in which "out of specification", "out of trend data" or "atypical data" was not reported because repeat testing results gave results that were either in specification or were more in line with the expected trend. I explained that retest results may only be reported after the original results have been invalidated. In all of the cases mentioned above, there were no scientific justifications for invalidating the original results.

All present for the closeout meeting agreed with this Observation.

OBSERVATION 2

The accuracy, sensitivity, specificity, and reproducibility of test methods have not been established.

Specifically, there is no assurance that methods are appropriate for use due to repeated testing without invalidating original out of specification data obtained during method validations. For example:

a) The accuracy & precision study was repeated in the method validation of related compounds testing for [redacted] however the original out of specification accuracy results for [redacted] were not invalidated.

b) The linearity & range study was repeated in the method validation of dissolution testing for [redacted] however the original out of specification results for percentage bias were not invalidated.

c) The accuracy & precision study was repeated in the method validation of related substances testing for [redacted] however the original out of specification accuracy results for Impurity-C were not invalidated.

d) The accuracy & precision study was repeated in the method validation of related substances testing for [redacted] however the original out of specification accuracy results for [redacted] were not invalidated.

Reference: 21 CFR 211.165(e)

Supporting Evidence and Relevance:

In reviewing Investigation [redacted] I noted that the accuracy & precision study was repeated in the method validation of related compounds testing for [redacted] **(Exhibit 15)**. The original results for the accuracy results of known related compounds were as follows:

Related Compounds	*Mean Recovery at*	*Mean Recovery*	*Mean Recovery at*
[redacted]			

The acceptance criteria for percent recovery at each level is [redacted] The investigation did not find an assignable cause for the recovery results for [redacted] which did not meet the acceptance criteria of the method validation study. The original out of specification accuracy results for [redacted] were not invalidated and the conclusion of the investigation stated "it has been decided to ignore the results obtained under above study and to re-perform the "Accuracy and Precision" study as per the procedure described in the protocol". I explained that the original data could not be ignored.

In reviewing Investigation [redacted] I noted that the linearity & range study was repeated in the method validation of dissolution testing for [redacted] however the original out of specification results for percentage bias were not invalidated **(Exhibit 16)**. The laboratory investigation was inconclusive, no assignable cause was identified and the conclusion of the investigation stated that "it has been decided to ignore these data and to re-perform "Linearity & Range" study." Again, I explained the original data could not be ignored.

The accuracy & precision study was repeated in the method validation of related substances testing for [redacted] however the original out of specification accuracy results for Impurity-C were not invalidated **(Exhibit 17)**. The original results for recovery of Impurity–C were as follows:

Level	*Mean % recovery*	*RSD*
[redacted]		

[redacted]

The acceptance criteria for mean percent recovery is [redacted] No assignable cause was identified for the high recovery results of Impurity–C in the laboratory investigation. The conclusion and recommendation indicated that the original results were invalid and to re-perform the accuracy and precision study. The study was repeated and the data is attached as **Exhibit 19.** I explained that there was no scientific justification for invalidating the original results.

The accuracy results for the related substance [redacted] at the [redacted] level in the method validation of related substances testing for Benztropine Mesylate, API. The acceptance criteria for average % recovery is [redacted] and the results for [redacted] concluded that "no assignable cause could be identified" and that "it has been decided to ignore the results obtained under above study and to re-perform "Accuracy and Precision" study as per the procedure described in the protocol" **(Exhibit 20).** Investigation [redacted] presents the repeat analysis for the Accuracy and Precision study **(Exhibit 21).** The average percent recovery for [redacted] levels were [redacted] respectively. I again stated that there was no scientific justification for the invalidation of the original results.

Discussion with Management:

I discussed that there is no assurance that methods are appropriate for use due to repeated testing without invalidating original out of specification data obtained during method validations. I explained that if there is no cause identified for the out of specification data, there is no reason that the original data should be considered invalid. I explained that if questionable data is generated during a method validation, then the method should be examined to see if the method itself is adequate. I explained that original results that fail to meet the acceptance criteria cannot be ignored. The original results must be invalidated before retesting results can be accepted. I also explained that there must be scientific justification for the invalidation of results.

All present at the closeout meeting agreed with this Observation.

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OBSERVATION 3

Verification of the suitability of the testing methods is deficient in that they are not performed under actual conditions of use.

Specifically, there is no assurance that equipment is adequately cleaned due to the deficiencies in cleaning validation studies. For example:

a) Cleaning validation was performed for the process trains of the following products without evaluating for sample recovery: [redacted]

b) Recovery studies were performed by applying a known amount of active pharmaceutical ingredient directly to a swab instead of applying the active to a coupon or template to replicate the equipment surface from which the active should have been swabbed. Cleaning validation was performed in this manner for the process trains of the following products: [redacted]

c) Cleaning Validation studies do not indicate whether or not a cleaning agent was used when cleaning the equipment process train. The current standard operating procedures DOI # [redacted] indicate that equipment could be cleaned "with hot water or with approved cleaning agent and water if needed". In addition, there are no studies to show the cleaning agent is effectively removed from equipment during the cleaning process.

Reference: 21 CFR 211.194(a)(2)

Supporting Evidence and Relevance:

In reviewing cleaning validations for multiple products, I noted that prior to late 2004 or early 2005, recovery studies were either not performed at all or were performed by directly applying a known amount of API to a swab instead of using the swab to remove a known amount of API from a template replicating the equipment. **Exhibit 22** shows that there was no testing of a swab for recovery in the Cleaning Validation Report for [redacted] There are currently no recovery studies for [redacted]

In the Cleaning Validation Report for [redacted] I noted that the recovery study was performed by adding [redacted] of the Active Pharmaceutical Ingredient (API) directly onto a cotton swab (**Exhibit 23**). I asked if the API had been applied to a template or a coupon, which would replicate the equipment surface, and then swabbed to show recovery capabilities. Mr. Shah

indicated that this had not been done. I explained that applying the API directly to the swab does not effectively represent the ability of the cotton swab to remove the active from the manufacturing equipment. I also noted that recovery studies were performed in the same way (API applied directly to cotton swab) for [redacted]

A list of recovery studies for cleaning validations was provided and is attached as **Exhibit 24**. Those listed without a completion date are those which have not yet been completed.

Cleaning Validation studies do not indicate whether or not a cleaning agent was used when cleaning the equipment process train prior to conducting the study. The current standard operating procedures DOI # [redacted] DOI # [redacted] indicate that equipment could be cleaned "with hot water or with approved cleaning agent and water if needed" (**Exhibit 25** and **Exhibit 26**). In addition, there are no studies to show the cleaning agent is effectively removed from equipment during the cleaning process. I explained the purpose of including detergent studies in the cleaning validations to ensure all detergent is adequately removed in the cleaning of equipment if it is in fact used in the cleaning of packaging equipment.

Discussion with Management:

I explained that the cleaning validations were inadequate due to the lack of recovery studies and the lack of clarification in cleaning procedures. Mr. Shah indicated that detergent is not used in the cleaning of packaging equipment. He explained that they were in the process of changing the cleaning procedures to reflect the fact that there is no detergent used on packaging equipment. He also explained that they were currently conducting the remainder of the recovery studies and that the firm was currently working with consultants from Protocol Link to review all cleaning validations and to set-up a matrix approach for future cleaning validation activities.

All present at the closeout meeting agreed with this Observation.

GENERAL DISCUSSION WITH MANAGEMENT

The following items were discussed both during the inspection and again at the closeout meeting. Present for the closeout meeting were:

Warehousing practices-

During the tour of the warehouse, I noted there were several items pulled from their assigned locations without any notation as to where they were going or why they were no longer located in their assigned locations. These items included PO# [redacted] PO# [redacted] PO# [redacted] and PO# [redacted] Management indicated that these items were supposed to have a staging page attached to the pallets indicating where these items were to be moved. I explained that it is important to attach the appropriate documentation to items once they are pulled from their designated locations in order to avoid any confusion and to prevent mix-ups.

Solution Stabilities-

In reviewing laboratory investigations, I noted that there were several instances in which related substances testing could not be repeated using the same standard and sample solutions because the solution stabilities had not been established. I indicated that it is important to address solution stabilities during method validations in order to facilitate in future laboratory investigations. I explained that it would be advantageous to use the original standard and sample solutions whenever possible when conducting investigations into atypical results. There is currently no solution stability data available in the Related Substances Method Validations for [redacted]

Equipment Qualifications-

During my review of equipment qualifications, I noted two instances in which the electrical service to a particular piece of equipment was found to be less than the acceptance criteria without a noted discrepancy in the qualification. For example, in the qualification of the King Tablet/Capsule Counter, Model TC12 (Equipment ID # 294), the minimum specification for electrical service is [redacted]V, but the actual service as found was [redacted]V **(Exhibit 27)**. In the qualification of the King Tablet/Capsule Counter, Model TC12 (Equipment ID # 296), the minimum specification for electrical service is [redacted]V, but the actual service as found was [redacted]V **(Exhibti 28)**. I explained that the discrepancies should have been noted during the equipment qualifications and a justification should have been provided to indicate why or why not these as found values were acceptable.

Preventative Maintenance-

In reviewing the qualification of the stability chambers, I asked to see preventative maintenance documentation. Mr. Shah indicated there was no procedure in place fro conducting preventative maintenance on the stability chambers. I explained a program should be put in place for the chambers.

All present at the closeout meeting agreed with these discussion items.

COMPLAINTS

Complaints were reviewed during this inspection. No deficiencies were noted.

REFUSALS

There were no refusals throughout the course of the inspection.

SAMPLES COLLECTED

No samples were collected during the course of the inspection

ATTACHMENTS

FDA 482, dated 9/18/06, 1 page
FDA 483, dated 10/11/06, 3 pages

EXHIBITS COLLECTED

1) Facility Diagram, 2 pages
2) Product List, 2 pages
3) Organizational Charts Pre-QSIP Assessment, 21 pages
4) Organizational Charts Post-QSIP Assessment, 21 pages
5) Laboratory Investigation Reference # [redacted]
6) Re-testing of [redacted] 4 pages
7) OOS Investigation Number [redacted] 3 pages
8) Investigation Report For [redacted] 11 pages
9) Laboratory Notebook pages for the [redacted]
10) The filter study completed on 5/31/06, 16 pages

11) Repeat testing for Related Substances, [redacted]
12) Investigation [redacted]
13) Investigation [redacted]
14) Investigation [redacted]
15) Investigation [redacted]
16) Investigation [redacted]
17) Investigation [redacted]
18) Laboratory Notebook pages for [redacted]
19) Laboratory Notebook pages for [redacted]
20) Investigation [redacted]
21) Investigation [redacted]
22) Cleaning Validation Report for [redacted]
23) Cleaning Validation Report for [redacted]
24) List of recovery studies for Cleaning Validations, 1 page
25) DOI # [redacted]
26) DOI # [redacted]
27) Qualification of the King Tablet/Capsule Counter, Model TC12 (Equipment ID # 294), 1 page
28) Qualification of the King Tablet/Capsule Counter, Model TC12 (Equipment ID # 296), 1 page

Kristy A. Zielny

Kristy A. Zielny, Investigator